



International Journal of Medical Research & Health Sciences

www.ijmrhs.com

Volume 4 Issue 1

Coden: IJMRHS

Copyright ©2014

ISSN: 2319-5886

Received: 3rd Oct 2014

Revised: 7th Nov 2014

Accepted: 24th Nov 2014

Research article

ACUTE EFFECT OF FLUCONAZOLE, ITRACONAZOLE AND VORICONAZOLE ON BLOOD GLUCOSE IN NORMOGLYCEMIC & DIABETIC RATS: AN EXPERIMENTAL STUDY

*Jadhav Amol, Nayak BB, Vakade Kiran P, Sanghishetti Vijay Prasad, Vijay Kumar AN, Vrushali Nibrad, Raul AR

Department of Pharmacology, Padmashree Dr. Vithalrao Vikhe Patil Foundation's Medical College, Ahmednagar, Maharashtra

*Corresponding author email: dramoljadhav1@gmail.com

ABSTRACT

Anti-fungal and antimicrobials are frequently co-prescribed either to manage or treat either the secondary complications or other diseases. Among antifungal drugs Fluconazole, Itraconazole & Voriconazole are most commonly used. The present study was undertaken to further confirm the effect of Voriconazole as well as other antifungal drugs on blood Glucose level. **Aim & Objectives:** 1. To Study the effect of Fluconazole, Itraconazole & Voriacozazole in Normoglycemic & Diabetic Rats on Blood Glucose. 2. To compare the effects between all drugs. **Material & Methodology:** Grouping: Animals divided into 8 groups in each group 6 animals. Group 1- 4: Normoglycemic rats, Group 5-8 Diabetic rats (alloxan induced) Group 1,5: received vehicle (Normal saline) Group 2,6: received Fluconazole (18mg/kg BW), Group 3,7 received Itraconazole (18mg/kg BW) Group 4,8 received Voriconazole (18mg/kg BW). The glucose levels were estimated by Glucometer method (Accu-check active) at the interval of 0, ½ hr, 1hrs, 2hrs & 4hrs after drug administration. **Results:** Effect on blood glucose in Normoglycemic Rats: Voriconazole had a significant hypoglycaemic effect which appeared after 1 hr ('p' value=0.0102) of administration & persisted up to 2 hrs ('p' value=0.0001). However effect of Voriconazole was found to be declined after 2 hrs. There was no significant change in blood glucose in normoglycemic rats with Fluconazole & Itraconazole. Effect on blood glucose in Diabetic Rats: (Table 2): Voriconazole had a significant hypoglycaemic effect which appeared after 1 hr ('p' value=0.013) of administration & persisted up to 2 hrs ('p' value=0.001) in acute studies. However effect of Voriconazole was found to be declined after 2 hrs. There was no significant change in blood glucose in diabetic rats with Fluconazole & Itraconazole treated. **Conclusion:** Itraconazole, Fluconazole can be safely used in diabetic with fungal infections. Voriconazole should be avoided in diabetics to minimise the further hypoglycaemia.

Keywords: Fluconazole, Itraconazole, Voriacozazole, Normoglycemic, Alloxan induced Diabetic rats

INTRODUCTION

Diabetes mellitus (DM) is a clinical syndrome associated with deficiency of insulin secretion or action. It is considered one of the largest emerging threats to health in the 21st century. It is estimated that there will be 380 million persons with DM in 2025¹. DM has been associated with reduced response of T cells, neutrophil function, and disorders of humoral

immunity. Consequently, DM increases the susceptibility to infections. Diabetics are immunocompromised; they are easily susceptible to a number of opportunistic fungal infections, which potentially increases their morbidity & mortality. The greater frequency of infections in diabetic patients is caused by the hyperglycemic environment that favours

immune dysfunction, micro- and macro-angiopathies, neuropathy, and decrease in the antibacterial activity of urine, gastrointestinal and urinary dysmotility, and greater number of medical interventions in these patients. The infections affect all organs and systems. In addition to the increased morbidity, infectious processes may be the first manifestation of diabetes mellitus or the precipitating factors for complications inherent to the disease, such as diabetic ketoacidosis and hypoglycaemia^{2,3}.

Anti-fungal and antimicrobials are frequently co-prescribed either to manage or treat either the secondary complications or other diseases. Among antifungal drugs Fluconazole, Itraconazole & Voriconazole are most commonly used. Voriconazole is the newest agent in the armamentarium against fungal infections. It is a triazole antifungal with a structure related to that of Fluconazole and a spectrum of activity comparable to that of Itraconazole. Voriconazole is indicated for the treatment of invasive aspergillosis and for the treatment of fungal infections caused by *S.apiospermum* and *Fusarium* spp that are refractory to other antifungal agents.³

There are some case reports suggesting Voriconazole have some effect on blood glucose in diabetic patients. Since Literature on this information is very scanty, the present study was undertaken to further confirm the effect of Voriconazole as well as other antifungal drugs on blood Glucose level in normoglycemic as well as diabetic rats^{4,5}.

Aim & Objectives: To Study the effect of Fluconazole, Itraconazole & Voriiconazole in Normoglycemic & Diabetic Rats on Blood Glucose. 2. To compare the effects between all drugs.

MATERIAL & METHODS

Six to eight weeks old male Wistar rats weighing 250-280grams were housed in polypropylene cages with stainless steel top grill containing autoclaved rice husk at an ambient temperature of $22 \pm 3^\circ \text{C}$ and relative humidity of $55 \pm 10\%$. They were exposed to 12:12 light-dark cycle and had free access to food and water ad libitum. Animals were fed standard laboratory diet.

The methods and procedures described in the present study have been reviewed and approved by the

Institutional Animal Ethics Committee (IAEC) and experiments were performed in accordance with the guidelines by CPCSEA.

Grouping: Animals divided into 8 groups in each group 6 animals.

Group 1-4: Normoglycemic rats

Group 1: Normoglycemic rats received vehicle (Normal saline)

Group 2: Normoglycemic rats received Fluconazole (18mg/kg BW)

Group 3: Normoglycemic rats received Itraconazole (18mg/kg BW)

Group 4: Normoglycemic rats received Voriconazole (18mg/kg BW)

Group 5-8 Diabetic rats

Induction of Diabetes: Diabetes was induced by using freshly prepared solution of Alloxan monohydrate dissolved in normal saline. (Procedured from Sd fine Chem Limited, Mumbai) Animals were fasted for 18 hrs before administration of Alloxan (100mg/kg I.P. Single dose). Hyperglycemia was confirmed by elevated glucose level determined at 48 hrs after I.P. injection of alloxan. Rats with blood-glucose levels above 250 mg/dl were considered as diabetic and selected for the study.

Group 5: Diabetic rats received normal saline

Group 6: Diabetic rats received Fluconazole (18mg/kg BW)

Group 7: Diabetic rats received Itraconazole (18mg/kg BW)

Group 8: Diabetic rats received Voriconazole (18mg/kg BW)

(All the above drugs are dissolved in normal saline and administered via Oral route with the help of feeding needle)

Glucose estimation: The glucose level was estimated by Glucometer method (ACCU-CHECK ACTIVE MODEL: GC) at the interval of 0, ½ hrs, 1hrs, 2hrs & 4hrs after drug administration. Blood glucose levels were expressed as mg/dl of blood. After the experiment blood sugar level of alloxan induced diabetic rats had been normalised with I.P. injection of insulin, if found elevated.

Statistical Analysis: Data obtained were subjected to computerized Graph pad version 3.06. Paired 't' test is used for group comparison. $P < 0.05$ was accepted as statistically significant.

RESULTS

Table 1: Showing effect various drugs on blood glucose level in Normoglycemic rats[§]

Drugs	0hour	½hour	1hour	2 hours	4 hours
Control	88.5± 4.7	87.6 ±3.8	87.7 ±4.02	86.8±4.61	88.8 ±3.6
Fluconazole (18mg/kg bw wt)	87± 2.9	94.3 ±2.44	98.3 ±2.5	96.2 ±3.49	101 ±2.2
Itraconazole(18mg/kg bw wt)	92.2±4.52	95.2 ±4.8	101.7 ±6.17	102 ±4.3	98.5 ±4
Voriconazole (18mg/kg bw wt)	87.8±3.17	83.2 ±3.38	76.7 ±1.9**	61.8±2.37***	74 ±2.35

Where, 'P' value of Paired 't' test is expressed as p<0.05 *, p<0.01 ** & p<0.001 *** (values expressed mg/dl, Mean±SEM)

Table 2: Showing effect various drugs on blood glucose level in Diabetic rats[§]

Drugs	0 hour	½ hour	1 hour	2 hours	4 hours
Control	470±25.05	466.8±24.5	467.3±24.0	468.2±25.5	470±26.84
Fluconazole (18mg/kg bw wt)	519.3 ±18.6	518.2± 19.4	522.3 ±19.9	522.2 ±20.6	518.5 ±17.8
Itraconazole(18mg/kg bw wt)	484.3 ±29.5	482.7 ±28.8	486 ±27.9	485.8 ±28.9	489.3 ±29.4
Voriconazole(18mg/kg bw wt)	468.5±10.33	440.8±11.2	374.7±29.4**	334±27.9***	401 ±19.9

Where, 'P' value of Paired 't' test is expressed as p<0.05*, p<0.01** & p<0.001*** (values expressed mg/dl, Mean±SEM)

[§]All are compared with their respective zero hour readings

Effect on blood glucose in Normoglycemic Rats

(Table 1): Voriconazole had a significant hypoglycaemic effect which appeared after 1 hrs ('p' value= 0.0102**) of administration & persisted up to 2 hrs ('p' value=0.0001***) in acute studies. However effect of Voriconazole was found to be declined after 2 hrs & there were no significant hypoglycaemic effect at 4 hrs. There was no significant change in blood glucose in normoglycemic rats with Fluconazole & Itraconazole treated.

Effect on blood glucose in Diabetic Rats: (Table 2):

Voriconazole had a significant hypoglycaemic effect which appeared after 1 hrs ('p' value=0.013***) of administration & persisted up to 2 hrs ('p' value=0.001***) in acute studies. However effect of Voriconazole was found to be declined after 2 hrs & there were no significant hypoglycaemic effect at 4 hrs. There was no significant change in blood glucose level in diabetic rats with Fluconazole & Itraconazole treated.

DISCUSSION

Hypoglycemia is a potentially fatal, condition. Common causes of hypoglycaemia in non-diabetics include drugs, chronic renal failure, alcohol intoxication, liver failure, sepsis, cancer and endocrine disorders. Drug-induced hypoglycemia can be severe and may cause significant morbidity. Voriconazole is a triazole antifungal agent. The

primary mode of action of Voriconazole is the inhibition of fungal ergosterol biosynthesis. Voriconazole has an oral bioavailability of 96%. In addition, there are reports indicating that Voriconazole a relatively newer antifungal agent to inhibit human cytochrome P450 enzyme system. The most important CYP isoenzyme that are inhibited or affected by antifungals like ketoconazole, and Voriconazole are CYP1A2, CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6. There is a possibility that drug-drug interaction may occur between the antifungals and the drugs metabolized by these enzymes^{6,7}.

A previous study has shown that the major metabolite, Voriconazole N-oxide, inhibits the metabolic activity of these enzymes and increases Voriconazole level.

Toxicity reported with Voriconazole includes changes in vision, hepatotoxicity, cognitive dysfunction and rash.⁸

This study is planned to study the effect of Voriconazole along with other commonly used antifungal drugs like Itraconazole & Fluconazole which belongs to the same triazole group in normoglycemic and alloxan-induced diabetic rats. The normoglycemic rat model served to quickly identify the effect and the diabetic rat model served to validate the same response in patho-physiological condition where this all antifungal drugs are most commonly used.

Sometimes, Polypharmacy is needed in some patients to treat disease conditions. When multiple drugs are used there are increased chances of drug-drug interactions. These types of drug-drug interactions occur more frequently in whom multiple drugs are used chronically. In all such conditions, it is a needed to make an attempt to readjust the dose &/or frequency of administration of any one or both the drugs.

Therefore, there is every possibility that drug-drug interaction may develop and may pose problems of either overdoses or ineffectiveness. So it is very much essential to evaluate the drug-drug interaction in those conditions. According to reports, the incidence of interaction ranges up to 20% in patients receiving more than 10 drugs. It is one of the leading cause of death.⁹

Earlier experiments have revealed that Voriconazole pre-treatment has enhanced the hypoglycemic effect of rosiglitazone and glipizide in both carnivorous and herbivorous species.¹⁰⁻¹² However, in the present experiment the influence of Voriconazole pre-treatment on the same drugs under pathophysiological condition i.e. Experimentally induced diabetes in albino rats was studied.¹³⁻¹⁵

We would like to place on record that the present study is carried out in Normoglycemic rats and diabetic rats. Therefore, we suggest that similar study should be conducted in healthy volunteers and diabetic patients to confirm the obtained results. It is further required to establish the influence of Voriconazole pretreatment on the pharmacokinetic parameters of oral antidiabetic agents in human volunteers.

CONCLUSION

Itraconazole, Fluconazole can be safely used in diabetic associated with fungal infections. Voriconazole should be avoided in diabetics to minimise the further hypoglycaemia.

Limitation the study:

1. Small Sample size, animal study only
2. Seen only acute effect (up to 4 hrs),
3. For the confirmation of above results requires further clinical trials
4. Interaction study to be done with known standard anti diabetic drugs

ACKNOWLEDGMENT: Our sincere thanks to management for providing the necessary facilities.

Source of funding: Nil

Conflict of interest: None declared by the authors

REFERENCES

1. Bjørnar Allgot, Delice Gan, Hilary King, Pierre Lefèbvre, Jean-Claude Mbanya, et al., Diabetes Atlas committee. http://www.idf.org/sites/default/files/IDFDiabetes_Atlas_2ndEd.pdf
2. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM) FEMS Immunol Med Microbiol. 1999;26:256–65.
3. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis. 2005; 41:281–8.
4. Boyd AE, Modi S, Howard SJ, Moore CB, Keevil BJ, Denning DW. Adverse reactions to Voriconazole. Clin Infect Dis. 2004;39:1241–4.
5. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Randomized comparison of Voriconazole and amphotericin B in primary therapy of invasive aspergillosis. N Engl J Med. 2002;347:408–15.
6. Nickie D. Greer. Voriconazole: The newest triazole antifungal agent. Proc (Bayl Univ Med Cent). 2003; 16(2): 241–248.
7. Nelson, Koymans L, Kamataki, Stegeman J J, Feyereisen R, Waxman DJ et al. P450 Super Family: Update on New Sequence, Gene Mapping, Accession Numbers and Nomenclature. Pharmacogenetics 1996; 6:1 42.
8. Murad MH, Coto-Yglesias F, Wang AT, Sheidaee N, Mullan RJ, Elamin MB, et al. Drug-induced hypoglycemia: A systematic review. J Clin Endocrinol Metab. 2009;94:741-5
9. Drug reactions a leading cause of death Available at: <http://www.rxmanagement.net/index.php/reason-one.html>
10. Study the pharmacokinetic drug interaction of voriconazole with oral anti-diabetic agents, H Sarah Priya & etal, International Journal of Pharmaceutical Sciences, May-August, 2011;3 (2): 1271-78

11. Mendoza A, Kim YN, Chernoff A. Hypoglycemia in hospitalized adult patients without diabetes. *Endocr Pract* 2005;11:91-6.
12. Goodman and Gilman's, *The Pharmacological Basis of Therapeutics*, 11th edition, McGraw Hill, New York; 2006
13. Agarwal R, Singh N, Amphotericin B is Still the Drug of Choice for Invasive Aspergillosis. Voriconazole Versus Amphotericin B for Primary Therapy of Invasive Aspergillosis. *Am J Respir Crit Care Med*. 2006; 174 (1): 102.
14. Patterson T, Boucher H, Herbrecht R, Denning D, Lorthalory O, Ribaud P, et al. Strategy of following Voriconazole Versus Amphotericin B Therapy with other licensed Antifungal therapy for Primary Treatment of Invasive Aspergillosis: Impact of Other Therapies on Outcome. *Clin Infect Dis*. 2005; 41 (10): 1448-52.
15. Kullberg B, Sobel J, Ruhnke M, Pappas P, Viscoli C, Rex J, et al., Voriconazole versus a Regimen of Amphotericin B followed by Fluconazole for Candidaemia in Non-neutropenic Patients: a Randomized Non-inferiority trial. *Lancet*, 2005; 366 (9495): 1435-42.